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The Fuzzy System as a Promising Tool for Drugs Selection in Medical Practice

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ABSTRACT The aim of this paper was to demonstrate the potential of the fuzzy system approach to the analysis of healthcare databases for clinicians in their routine daily practice. The healthcare data about 50 000 medical prescription items for 38 990 individual patients and 2601 various codes of diagnoses categorized according to Slovak version of the tenth revision of the International Statistical Classification of Diseases and Related Health Problems were used for the retrospective study. The fuzzy system approach was applied to the analysis of medical prescription items for I10.90 and E11.90 comorbid patients as the most frequently identified cardiovascular and endocrine codes of diagnoses. Nearly 64% of co-identified I10.90 and E11.90 patients were associated with other additional diagnose. According to the fuzzy system approach, the metformin or glimepiride in combination with moxonidine, metoprolol, or amlodipine was identified as the mainstream drug preferences and/or individual ''know-how'' of clinicians in pharmacotherapy of mentioned polymorbid patients from 21 various active substances. The results of this paper suggest that the fuzzy system approach to healthcare data obtained from insurance companies may be a helpful way of generating information useful for final decision process in the drugs selection for similar polymorbid patients in medical practice. The obtained data can be used as recommendations for other and/or for less experienced clinicians in drugs selection for patients with similar (or unusual) combinations of diagnoses as well as in clinical situations where the ''golden'' pharmacotherapeutic standards have not been precisely specified or are totally absent for multi-comorbid patients.

INDEX TERMS Decision-making process, drugs delivery, fuzzy system, health information management, patient monitoring.

I. INTRODUCTION

Effective pharmacotherapy is based on the drugs prescribed in relevant medicinal products suitable for the patient's current diagnosis or a combination of diagnoses. The clinical decision support software always involved some type of up-to-date passive electronic drug reference database based on data from drug handbooks, pocket cards, published scientific papers or approved by ''Summary of Product Characteristics (SPC),'' which described drug indications, contraindications, doses and interactions. However, the above-mentioned sources used for drug databases do not describe the diagnoses in a uniform manner according to the International Statistical Classification of Diseases and Related Health Problems (ICD). Moreover, the approved SPC do not mention drug indications, which are not licensed but are usually clinically be used as ''off-label.'' Besides, some degree of variability may still exist between licensed indications or frequency of drugs side effects of medicinal products produced by several pharmaceutical companies with regard to the same active substance. In this case, the processing and evaluation of drug data is more than problematic [1], [2].

On the other hand, the knowledge of individual clinicians about clinical effects of applied drugs in everyday practice reaches a statistical significance in time with the number of drug (co-)applications to individual patients. Moreover, data are generally statistically significant among the clinicians because the numbers of treated patients and drug application occurrences are high. Although these data are available in

healthcare databases of insurance companies, they are not systematically summarized in an available database, so it is not possible to establish rules for any expert system. Moreover, the setting up of such a database is problematic also for unrealistic way to ask each clinician for the reason why she/he decided to apply a selected drug (or drug combination) in a selected case. In the reference [3] two methods – Loewe Additivity and Bliss Independence – are used to determine the combination of drugs (Quantifying Synergistic Drug Combinations). The Loewe Additivity method needs information about the concentration of inhibitors in the drug and it investigates overall inhibition of the resulting combination. Bliss Independence models statistically compute predicted combined effects of drug A and B as a product of individual effects with drugs A and B. Because the combination of drugs gives enormous number of possible drug combinations, strategies to reduce search space and prioritize experiments are needed [4], [5].

In this case, the potential of fuzzy logic principles in which the variables in the system are represented and manipulated in a binary manner may be applied. The variables may be defined in discrete terms while the transition between discrete terms can be gradual. A value for a variable might partially belong to a set and have a degree of membership anywhere between 0 and 1 and thus it can partially belong to several sets with the total membership adding to one [6]. The fuzzy system have the structure of a series of ''if-then''-rules to form knowledge base and fuzzy rules present mathematical relationships mapping inputs to outputs [6], [7]. Although the fuzzy logic is not appropriate in all cases like in linear system models or if there are large amounts of missing data [3], [6], the several successful applications of the fuzzy principles in medical practice [7]–[11] with special regard to pharmacology have already been recently described [6], [9], [12]–[14]. The potential of the fuzzy system approach to the drug-prescribing analysis according to the anatomical therapeutic chemical (ATC) classification system among clinicians has already been used but only in the analysis of their regional prescribing patterns [15]. As mentioned in the literature [16], the recommended systems based on fuzzy logic currently present successful solutions to facilitate access for online users to the information fitting their preferences. Collaborative filtering systems can generate recommendations only using users' ratings and without any need for additional information. Collaborative filtering focuses on suggesting to the target user the items that are already preferred by other users with similar preference patterns.

In contrast to this, the aim of this study was to demonstrate the potential of the Sugeno fuzzy model based system which for acquisition of information basically allows the use of both implicit expert knowledge of physicians as well as of a drug database obtained from the State Institute for Drug Control in Slovakia for the Quantifying synergistic drug combinations. The fuzzy approach to analysis of healthcare databases represents a new tool for creating information that is useful for final decision-making process of drug selection for defined polymorbid group of patients in medical practice.

II. METHODS

In the literature [17], two levels of classification (taxonomy) for the fuzzy system software are proposed. The first level represents the software developed according to the aim for which it was developed – this is the purpose-based taxonomy. Standardized software by the type (library, toolbox, and so on) presents the second level. In terms of this classification, we can include the proposed first-level expert system into the ''Fuzzy Systems Software for Specific Application Purposes'' category, designed for Solving Specific Problems of Pharmacy. From view of the second level, we can rank it into the category ''General-Purpose Fuzzy Systems Toolboxes,'' namely the Sugeno fuzzy system.

The healthcare data about the total of 50,000 medical prescription items for the retrospective study were obtained from the second largest Slovak insurance company as cvs files and they covered the period of 9 months (from December 2014 to August 2015). The healthcare data in each row included a seven-digit digital anonymous code of individual patient, its gender and age. Besides, the code of the patient diagnoses, categorized according to Slovak version of Tenth revision of ICD (ICD-10-Sk) [18] was available. The individual prescribed active substances according to the ATC classification system and trade names of dispensed medicinal products defined by State Institute for Drug Control codes were accessible. The additional information covered dispensed quantity of medicinal products, the date of dispensation and specializations of prescribed clinicians. The medical prescription items were prescribed for the group of 38,990 individual patients and 2,601 various ICD-10-Sk codes of diagnoses. For the sake of clarity, the fuzzy system approach was applied to the analysis of medical prescription items for polymorbid patients with the most frequently identified cardiovascular and endocrine ICD-10-Sk codes. The term of polymorbid patients was used for patients with two or more verified recorded diagnoses. In Slovakia, the health insurance is obligated for all residents and is financed by means of social contributions of employers, employees and the state. The residents can freely choose from one state and two commercial insurance companies that pay health care in the same amount and scope.

The proposed fuzzy concept was based on the following assumptions:

1) Experiences and knowledge of clinicians (''know-how'') were expressed in their decisions for prescription of drugs combination for a certain patient diagnosis.
2) A quantitative relation exists between a certain combination of diagnoses and the suitability of a particular drug application for its treatment.
3) With the concurrent application of two or more drugs there was a relation between the suitability of combination of their diagnoses, and this relation quantitatively

defines the suitability of application of their mutual combination.

4) The more frequently a certain combinations of drugs occurred in the prescriptions for a certain combination of diagnoses, the more it was preferred for their treatment by clinicians.

TABLE 1. Setting up of example of initial knowledge database from healthcare data.

Patient	Date	L1	L2	L3	L4	D1	D2	D3
P1	1.5.2015	0	0	1	0	0	1	0
P2	2.5.2015	0	1	0	0	1	0	0
P3	3.5.2015	0	1	1	1	0	1	1
P4	4.5.2015	0	0	1	1	0	1	0
P5	4.5.2015	0	1	1	0	1	0	0
P6	4.5.2015	0	1	0	1	0	0	1
P7	5.5.2015	1	0	1	1	0	1	1
P8	6.5.2015	0	1	1	0	0	1	1
P9	6.5.2015	0	0	1	1	1	1	0
P10	6.5.2015	0	1	0	0	1	0	0

TABLE 2. Co-occurrence of drugs and diagnoses and their quantitative expression in the range of < 0, 1 >.

	L1		L2		L3		L4		D1		D2		D3	
	No	QR	No	QR	No	QR	No	QR	No	QR	No	QR	No	QR
L1	4	1.00	0	0.00	1	0.25	1	0.25	0	0.00	1	0.25	1	0.25
L2	0	0.00	13	1.00	3	0.23	2	0.15	3	0.23	2	0.15	3	0.23
L3	1	0.25	3	0.23	19	1.00	4	0.21	2	0.11	6	0.32	3	0.16
L4	1	0.25	2	0.15	4	0.21	15	1.00	1	0.07	4	0.27	3	0.20
D1	0	0.00	3	0.23	2	0.11	1	0.07	7	1.00	1	0.14	0	0.00
D2	1	0.25	2	0.15	6	0.32	4	0.27	1	0.14	17	1.00	3	0.18
D3	1	0.25	3	0.23	3	0.16	3	0.20	0	0.00	3	0.18	13	1.00

No = number of co-occurrence
QR = quantitative expression of the relation (distance)

Algorithm for the sequence of obtaining information on the relations between drugs and diagnoses was based on:

1) Setting up a knowledge database for a specific drug or diagnosis. Table 1 demonstrates the example of initial database for 4 drugs (L1–L4), 3 diagnoses (D1–D3) and 10 patients (P1–P10) where L4 drug was prescribed 5 times, together with L1 drug that was prescribed once, with L2 drug that was prescribed twice, for diagnosis D2 which was prescribed four times, etc.
2) Modification of the knowledge database and determination of the universe (selecting only the diagnoses that occur in sufficient quantity and within the defined time interval) for the individual drug (diagnosis). Dividing the co-occurrence of two drugs by the total number of occurrences (expressed diagonally in yellow color in Table 2 of the drug (ratio against the diagonal) we obtain a value within the range of <0, 1>. The zero (0) value means that the two drugs never occur together, the one (1) value means they always occur together. This value can be understood as a "quantitative expression of the relation (distance)" between two drugs. Besides, for each drug there can be defined the set of drugs (and diagnoses) with which the drug had so far co-occurred. It is intuitively clear that if drugs <L2, L3> are "close," and at the same time drugs <L2, L4> are "close" and at the same time drugs <L3, L4> are "close," then also drugs <L2, L3, L4> will be mutually "close."
3) Compiling a distance table for co-administered drugs (Table 2).
4) Determining the fuzzy relation between drugs and diagnoses in the form of its fuzzy representation FIS (fuzzy inference system) – the quantitative value of the fuzzy relation depends on their mutual occurrence (Fig. 1).

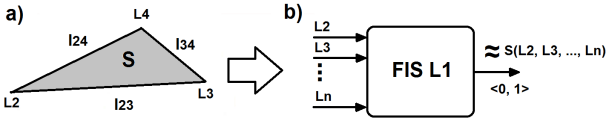

FIGURE 1. Graphic expression: (a) of mutual relation of drugs L2, L3, L4; (b) fuzzy representation of drug L1.

The quantitative expression of the mutual closeness of a triplet of drugs is a function of the closeness of the individual pairs expressed as the area of the "S" triangle (Fig. 1(a)). In general, the quantitative expression of mutual closeness (i.e. of the suitability or relation of mutual combination defined by clinicians) of an n-tuple of drugs is their mutual relation in (n-1) dimensional space (Fig. 1(b)) for the fuzzy representation of drug L1.

It is rather a problem to determine this relation analytically as the set of drugs is not organized. It seems a suitable tool for determining such relation consists in its fuzzy representation, i.e. a mathematical description by means of a set of fuzzy rules between its inputs and outputs. For example, for drug L1 its fuzzy representation would be FIS (Fuzzy Inference System) L1 (and thus the quantitative value of the relation S (L2, L3, L4)) expressed by seven rules from Table 2 in the form:

1. If L2 then $S = 0.00$,
2. If L3 then $S = 0.25$,
3. If L4 then $S = 0.25$,
4. If L2 and L3 then $S = 0.23$,
5. If L2 and L4 then $S = 0.15$,
6. If L3 and L4 then $S = 0.21$
7. If not L2 and not L3 and not L4 then $S = 0$.

and its fuzzy Sugeno type representation would be in the form as shown in Fig. 2.

For the drug combination [L1 L3] (which is expressed in the representation by the entry combination $L2 = 0$, $L3 = 1$, $L4 = 0$) the representation yields suitability of application of 0.25, which is precisely in line with Table 2.

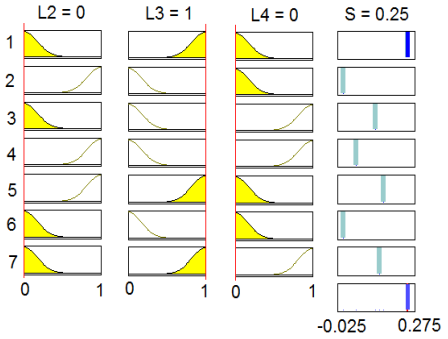

FIGURE 2. Fuzzy representation of drug L1 for combination with L3.

For the three-drug combination [L1 L2 L4] this representation yields suitability of application 0.15, which is also in line with Table 2, as illustrated in Fig. 3.

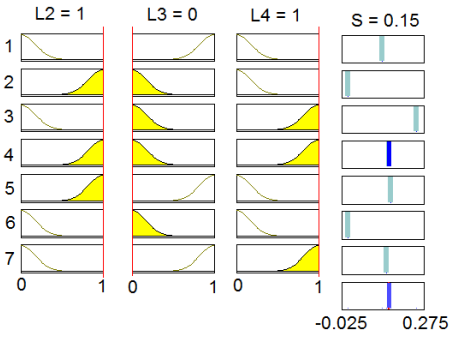

FIGURE 3. Fuzzy representation of drug L1 for three-drug combination with L2 and L4.

By compiling a pre-processed ''fuzzy representation'' of each drug (diagnosis) in the form of Table 2, or the fuzzy representation as in Fig. 2 and Fig. 3, one will obtain a quantitative expression of its relations (relationships, number of applications, distances) with other drugs and diagnoses.

Note: For the sake of clarity, the ''sharp'' (crisp) information has been used at development of the fuzzy system, and in this case the fuzzification result is the same as in Table 2. Using fuzzy information, the result would not be the same, but the designed fuzzy system could handle it.

The fuzzy evaluation of combinations of drugs or diagnoses was based on the:

1) Consolidation of universes for individual drugs, and
2) Fuzzy inference for a group of drugs and was performed in MATLAB ® software (version 2016A).

III. RESULTS

Oracle Database System Oracle Corporation, based on a standard PS of the type HP Z4 G4 with 16 GB DDR4 memory and a 1 TB (7200 rpm) hard disk, was chosen for specific implementation of the proposed expert system. The database of input data about drugs, recipes, and patients collected during one year period and having the size of 2.93 GB was obtained from a health insurance company.

In the first stage of data processing, relevant interactions between drugs and diagnoses were found using PL/SQL language and based on these a fuzzy image of each drug in the table form was created. Thus, approximately 4500 fuzzy images (tables) of different sizes were obtained; these presented a fuzzy image database of individual drugs.

In the second phase a script was created which, based on the given input combination of drugs and the database of their fuzzy images, calculated the fuzzy image of the overall mutual situation of the drugs (e.g., see Tab.2). This allows to determine the weight of their mutual occurrence and thus the suitability of their mutual prescription.

For the case study the database was reduced to 50,000 records, so it was possible to apply the Microsoft Office Access2007 database engine to create fuzzy images of the drugs and for processing of these images an m-file of the MATLAB 2013b package was used.

The most frequent cardiovascular diagnosis identified according to ICD-10-Sk was unspecified primary hypertension without hypertensive crisis (I10.90), present in 2.7 % of all analyzed patients (Table 3).

TABLE 3. Analyzed subgroup of polymorbid patients by the fuzzy system approach.

Code of diagnosis according to ICD-10-Sk[b]	Number of patients	Patients with more than one other code of diagnosis according to ICD-10-Sk (%)	Number of other identified code of diagnoses according to ICD-10-Sk	Number of active substances in ATC[a] classification system
I10.90[c]	1085	33	171	198
E11.90[d]	334	36.5	84	116
I10.90 and E11.90	11	63.6	6	21

[a]ATC = The anatomical therapeutic chemical classification system.
[b]ICD-10-Sk = Slovak version of Tenth revision of International Statistical Classification of Diseases and Related Health Problems.
[c]I10.90 = unspecified primary hypertension without hypertensive crisis.
[d]E11.90 = compensated Type 2 diabetes mellitus without complications.

The most frequent endocrine diagnosis identified according to ICD-10-Sk compensated Type 2 diabetes mellitus without complications (E11.90), presented in 0.9% of all analyzed patients. The group of patients with I10.90 diagnoses were treated with overall 198 various active substances (Table 3). On the other hand, the group of patients with E11.90 diagnoses were treated only with 116 various active substances (Table 3).

In the analyzed subgroup of polymorbid patients with co-identified I10.90 and E11.90 diagnoses, the total of 21 various active substances were found (Table 3, Table 4).

Nearly 64 % of these patients were also associated with other additional diagnosis (Table 3, Table 4). According to the fuzzy system analysis for E11.90 and I10.90 polymorbid patients, the most preferred prescription identified was that of metformin or glimepiride in combination with moxonidine, metoprolol or amlodipine (Table 4).

In more detail, the most frequent identified antidiabetic active substances for E11.90 patients with only

TABLE 4. The fuzzy analysis of prescribed active substances in E11.90 and I10.90 polymorbid patients.

Active substance according to ATC[a] classification system	Patient											Active substance related to code of diagnosis in E11.90[b] and I10.90[c] comorbid patients	Defuzzified values of the fuzzy results in E11.90 and I10.90 comorbid patients
	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9	No. 10	No. 11		
Metformin	x		x	x	x	x	x	x		x	x	E11.90[a]	0.236842
Gliclazide									x				0.026316
Glimepiride		x		x	x			x					0.105263
Metformin and Sitagliptin		x											0.026316
Acetylsalicylic acid		x										I25.9[d]	0.026316
			x									I10.90	0.026316
Ivabradine							x						0.026316
Moxonidine	x		x										0.052632
Metoprolol								x	x				0.052632
Betaxolol		x											0.026316
Carvedilol										x			0.026316
Amlodipine						x					x		0.052632
Nitrendipine			x										0.026316
Perindopril					x								0.026316
Quinapril and diuretics			x										0.026316
Perindopril and amlodipine				x									0.026316
Irbesartan and diuretics							x						0.026316
Atorvastatin			x			x		x				E78.0[e]	0.078947
Amoxicillin and enzyme inhibitor				x								J11.8[f]	0.026316
Aceclofenac				x								M16.0[g]	0.026316
Piroxicam				x								M51.1[h]	0.026316
Promethazine				x								J11.8	0.026316

I10.90 diagnoses were metformin and gliclazide (Table 4). Moreover, metformin was also the most frequently identified active substance in E11.9 and I10.90 patients with other additional diagnosis (Table 4). On the other hand, metoprolol, amlodipine and moxonidine were the most frequent identified antihypertensive active substances for E11.90 and I10.90 patients (Table 4).

IV. DISCUSSION

In our experimental retrospective study in which the potential of the fuzzy system approach to analysis of healthcare databases was used, the metformin or glimepiride (as antidiabetic drugs) in combination with the metoprolol, amlodipine or moxonidine (as antihypertensive drugs) was identified as the most appropriate for E11.90 and I10.90 comorbid patients from the real health insurance database.

According to the international guidelines, the beta blockers (BB) or calcium channel blockers (CCB) belong to the rationale drug class of choice in the treatment of hypertensive diabetic patients [19], [20]. They are also recommended by The Commission for Rational Pharmacotherapy and Drug Policy of The Slovak Ministry of Health [21]. They are also recommended by The Slovak Society of Cardiology [21]. Besides, the CCB and BB were the second and third preferred group of antihypertensive drugs after angiotensin-converting enzyme inhibitors (ACEI) in everyday practice of questioned general practice doctors in Slovakia in the treatment of hypertensive patients [22] and were preferred groups of antihypertensive monotherapy in primary care of hypertensive diabetic patients [23]. Although the risk of major vascular events was significantly reduced in ACEI treated hypertensive patients with type 2 diabetes compared to amplodipine ones [24], it seems, that the benefit of amplodipine prevents early atherosclerotic lesions in mentioned patients as it was demonstrated by decreasing the intimal-medial thickness of the common carotid artery [25].

On the other hand, the blood pressure lowering effect of amlodipine was comparable with the metabolically also neutral ACEI in hypertensive patients with type 2 diabetes [24], [25].

The meta-analysis of randomized clinical trials revealed that systolic and diastolic blood pressure lowering effect of amlodipine monotherapy was also comparable with the metoprolol monotherapy of hypertensive patients [26].

On the other hand, the data of the double-blind multicenter randomized study with metoprolol and moxonidine indicated effective comparable blood pressure control in hypertensive patients with type 2 diabetes although the long-term treatment with moxonidine seem to be more suitable for decrease of global vascular disease risk associated with glucose and lipid metabolism [27]. In comparison to metformin, the moxonidine was able to improve insulin

utility in hypertensive patient with impaired glucose tolerance although was not able to reduce HbA1C level [28]. In the same groups of patients, the moxonidine as well as metformin was able to improve significantly Matsuda insulin sensitivity index, significantly reduced body mass index and normalized blood pressure [28]. Although the metformin compared to glimepiride did not significantly reduce important metabolic risk factors of atherosclerotic vascular disease in normotensive diabetic patients [29], the metformin seems to be preferred therapy than sulfonylureas for diabetic patients with cardiovascular comorbidities including hypertension for significantly more effective reducing strokes [30], [31] and non-fatal cardiovascular events [32].

As our results illustrated, the analysis of obtained healthcare databases by the fuzzy system approach can identify mainstream drug preferences of clinicians and/or individual experience (''know-how'') of clinicians in pharmacotherapy of polymorbid patients with selected (defined) groups of individual diagnoses. As we discussed above, the obtained results must be always carefully verified. Moreover, the elimination of inadequate data associated with real clinical mistake decisions, which ones can be identified as frequent (or rare) and may be (or not) recommended, must be considered. Only after this consideration the results can be used as recommendations for other and/or for less experienced clinicians in drugs selection for polymorbid patients with similar (or unusual) combinations of diagnoses. In frequent combinations of diagnoses, specific patient characteristics and main clinical parameters of patients may be added to the fuzzy system algorithms in the final drug decision-making process. Moreover, the obtained data about the administered drugs in selected diagnoses may be additionally or simultaneously be analyzed by computerized databases for elimination of relative or absolute drug contraindications as well as for elimination of serious and harmful drug-drug interactions. Another advantage of the presented fuzzy system approach to large healthcare databases can consists in drug selection/recommendation for clinicians in clinical situations where the ''golden'' pharmacotherapeutic standards have not been precisely specified or are totally absent for individual groups of multi-comorbid patients. For group of patients with rarely combined diagnoses or in case of short time use of recently registered drug in clinical practice, the obtained suitability identified by the fuzzy system as low or zero must be carefully interpreted. In this case, a follow up comment may be added to the databases.

The expert systems based on crisp data do not allow to simply combine information from experts with information retrieved from the recipes database. Considering the philosophy of the proposed system, it is not a matter of principle to add information obtained from the State Institute for Drug Control to the fuzzy pictures of individual drugs and diagnoses in the first step of the algorithm at its compounding (where ''1'' is assigned for the recommended diagnosis and ''0'' is assigned for a forbidden diagnosis or drug).

Similarly, information from the manufacturer or expert can be added to the fuzzy image of each individual drug or diagnosis by adding an appropriate rule (a relation) and a function of relevance (quantitative relation rating) considering another drug or diagnosis.

In case the information database would be built only on crisp data, it is possible to achieve the same results using other methods of processing. Because of the fact that the information is always inserted into the database also in a linguistic way (by producers, experts), the use of the fuzzy system is justified by the fact that it can easily combine crisp information with information containing uncertainties.

When processing more complex large-scale databases (e.g. from health insurance companies), professional database systems have to be employed for pre-processing of data (creating fuzzy representations of particular database components), which only needs to be carried out once over a longer period of time, e.g. a year. The created fuzzy models can then be easily implemented and used on standard PCs, e.g. in pharmacies and in doctors' offices.

V. CONCLUSION

The results of this study suggest that the fuzzy system approach to obtained healthcare data from insurance companies may be a helpful way of generating information useful for final decision-making in the drugs selection process for similar polymorbid patients in medical practice.

The analysis of obtained healthcare databases by the fuzzy system approach can identify mainstream drug preferences of clinicians and/or individual experience (''know-how'') of clinicians in pharmacotherapy of polymorbid patients with selected (defined) groups of individual diagnoses.

The results can be used as recommendations for other and/or for less experienced clinicians in drugs selection for polymorbid patients with similar (or unusual) combinations of diagnoses.

The advantage of the fuzzy system approach to large healthcare databases can be drug selection/recommendation for clinicians in clinical situations where the ''golden'' pharmacotherapeutic standards have not been precisely specified or are totally absent for individual groups of multi-comorbid patients.

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